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SERVICE of INDUSTRIAL PROPERTY

Novel neuralgic associations with improved tolerance.

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The present invention relates to novel neuralgic associations with improved tolerance.

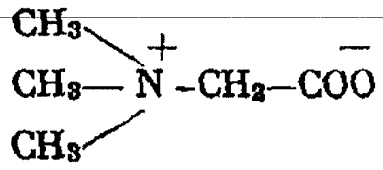
We know that the use of acetylsalicylic acid in treatment can lead to gastrointestinal incidents and in particular, irritation of the gastric mucosa caused by contact with acid particles of aspirin, when ingested. Thus, experimentally doses of 40 to 50 mg per os, caused in rats after few hours attaint of the stomach mucosa characterized by congestion and presence of bleeding dots and streaks; histologically, there are lesions of acute gastritis with an abrasion of the mucosa causing an inflammatory reaction in the underlying tissues.

To overcome these drawbacks, it has advocated the addition to pharmaceutical forms of neutralizing substances (such as sodium hydrogen carbonate, magnesium, calcium carbonate, alumina), or buffer substances, notably glycocol and its alumni derivatives and ornithine, or, finally, the simultaneous addition of these two types of substances.

However, the role of these additives is limited to solubilize and

dabbing acetylsalicylic acid without bringing themselves particular pharmacological properties to the achieved associations.

Among the substances that may effectively buffer acetylsalicylic acid, trimethyl-carboxymethyl-ammonium of formula:



is of particular interest.

Its buffering capacity is, in effect, equivalent to that of glycocol and it can easily form salts with organic acids whose buffering potency is also high.
In addition, this base provides interesting pharmacological properties in the specific case considered here:

Per os, it is devoid of systemic toxicity, which allows for long administration.
It does not inhibit peptic secretion.

It has a favorable effect on the retention of hepatic lipids reported during long-term and intensive treatment by acetylsalicylic acid, and a regularization of the metabolism of this same acid by action on liver conjugation.

These products allow the preparation of pharmaceutical formulations based on acetylsalicylic acid, well-buffered and in association with the aforementioned mineral salts, a total solubility in water of the same acid, which allows the administration of non aggressive buffered solutions to the gastric mucosa and with a pH which can be kept within the limits where peptic activity is not significantly changed.

In order to use in combination with aspirin, we have précised in a first step some properties of trimethyl-carboxymethylammonium and of some of its organic salts:

Acute toxicity: Doses of 2.40 g/ kg base intravenously are well supported by the rat. Per os, it is impossible to determine the LD 50 and LD 100 on the mouse and rat and the same goes for citrate;

Chronic toxicity: oral administration to rats for three months at a daily dose of 0.5 g/ kg basis and 1 g) kg citrate is well tolerated. The histological verification of the principal organs showed no anatomical damage. In particular the gastric mucosa was intact, at both macroscopic and histologic examinations;

The activity buffer trimethyl-carboxymethylammonium and some of its organic salts has been studied in pure aqueous solution and the normal artificial gastric juice in vitro.

Regarding the base its buffering potency is equivalent to that of glycol.

In pure aqueous solutions, for a salt such as citrate at 10% concentration, adding 12.5 ml of hydrochloric acid N (426.25 mg real HC1) is required to pass from initial pH of 2.6 to pH 1.2: this buffering capacity is hence much higher than that of citric acid alone in equivalent quantity (1.7 ml HC1 are only used).

In artificial gastric juice (USP formula XVI) (volume 150 ml) with citrate at 4% concentration, 16.1 ml of hydrochloric acid N (587.65 mg real HC1) are needed to lower the pH from its initial value of 2.1 to pH 1.2. Under the same conditions, to raise the pH values to 3.5 and 4.0, it is necessary to use 24 ml and 32.5 ml of sodium hydrogen carbonate N respectively, which corresponds to 2016 mg and 2730 mg NaHCO3.

The study of buffering activity with Bateson method, which more closely simulates normal physiological conditions, led to similar

conclusions: citrate maintains pH value to a fairly constant value during one hundred and twenty minutes at 37 °, despite the constant input of fresh artificial gastric juice.

These facts clearly demonstrate the high buffering capacity of trimethyl-carboxymethylammonium whose aqueous solutions of organic salts would suffer only of small changes in pH by the addition of strong acid or mineral base, thereby this buffering capacity being totally distinct from that much lower of the combined organic acid.

The pH area where this buffering capacity can exert is equivalent to the optimum area where pepsin proteolytic action can be the most favorably exerted.

In vitro action on the proteolytic activity of gastric juice.

During the absorption of buffering or antacid substances, protein digestion in the stomach can undergo significant changes as a result of the alteration of proteolytic pepsin properties during stomach digestion, proteolytic activity being constantly lowered.

We were able to verify that the trimethyl-carboxymethyl-ammonium and its citrate do not bring any disturbance in the digestion of proteins in vitro when using continuous infusion method described by Milani and his colleagues. The digestibility indices grouped in Table I give the mean values obtained for example with citrate and normal as hydrochlorhydric artificial gastric juices.

It can be seen that citrate not only restores a normal digestion in hydrochlorhydric gastric juices but slightly improves proteins digestion in gastric juices whose hydrochloric acid concentration is normal, this in a constant manner.

We observe similar facts with regard to the base, especially in the case of hyperchlorhydric gastric juice.

A study on the proteolytic activity of gastric juice collected in

humans after injection of histamine led to comparable results.

It should be also noted that gastric juices are maintained by these products in an area of favorable pH despite the wide variation of acidity or alkalinity during digestion. Their use is not likely to raise the pH to values incompatible with a normal digestion.

TABLE I

In vitro digestion Index
(artificial gastric juice)

	60 minutes	120 minutes	180 minutes
Normal gastric juice.....	0.95	0.96	0.93
+ 4% trimethyl-carboxymethyl-ammonium citrate.....	1.01	1.04	1.01
Hydrochlorhydric gastric juice.....	0.09	0.11	0.12
+ 4% trimethyl-carboxymethyl-ammonium citrate.....	0.90	0.90	0.88

Lipotropic Hepato-protective action.

Some authors have reported that during prolonged and intensive salicylates treatment, one can observe a hepatic lipid accumulation. On the other hand, the liver is involved in salicylic acid metabolism, which is notably submitted to a break by an esterase accelerating its hydrolysis, followed by the usual conjugations.

It seemed therefore desirable that, during acetyl salicylic acid prolonged or intensive administration, liver function must be fully corrected and that is what achieves carboxymethyl-trimethyl-ammonium which is a powerful and steady hepatoprotectant as well as a lipotropic.

Thus, in regard of hepatoprotection, parallel studies have shown that as base or organic salts forms, it protects guinea pig liver against carbon tetrachloride massive intoxication, such hepatoprotection being conveniently measured by Bromosulfonephtaleine time to onset in biliary excretion, as well as its rate of elimination in thirty and sixty minutes.

Doses of two to three thousandths of a molecule by intraperitoneal route are sufficient to restore normal rates of excretion of BSP, as well as a correct time to onset.

Lipotropic activity of carboxymethyl-trimethyl ammonium has been the subject of many studies.

In administering orally for a period of thirty days to Wistar race male rats, a dose of 200 mg/ kg of acetylsalicylic acid, we get a discreet but fairly constant hepatic steatosis (total lipid levels, 28% dry liver) compared to control rats. Simultaneous administration of trimethyl-carboxymethyl-ammonium at a dose of 500 mg/ kg protects animals, the percentage of total lipids being 20.5% of dry liver, rates similar to that of control groups of 19.1%.

Gastric mucosa Tolerance for acetylsalicylic acid trimethyl-carboxymethylammonium association.

By experimenting on white Wistar rats a drug formulation, for example formula N°. 5 below, at doses equivalent to 50 mg acetylsalicylic acid, it was not possible to identify (nor macroscopic or histological examination) lesions of the gastric mucosa, while pure acetylsalicylic acid administered at the same dose, under the same conditions, resulted in 80% hemorrhagic lesions in animals and at histologic examination resulted in gastritic lesions that caused an inflammatory reaction of the underlying tissues.

Dosage Forms. The trimethyl carboxymethyl ammonium in form of base or organic salt can easily be associated with acetylsalicylic acid,

either alone or with alkaline substances in water soluble effervescent forms or not, said forms being possibly associated with various complementary medicinal substances whose principal is represented by ascorbic acid. By judiciously combining the proportions of the various constituents, it is possible to obtain, upon dissolution, aqueous solutions whose pH remains compatible with a normal digestion.

Thus, we could prepare the following pharmaceutical forms: powders, granules, effervescent tablets or not, pills with normal coating or with gastric juice action resistant coating.

For example illustrative formulations, as described below, were easily prepared.

Formula nº 1 - Powder	g
Trimethyl-carboxymethyl-ammonium citrate	0.500
Acetyl salicylic acid	0.300 to 0.500
Magnesia	0.065 to 0.100
Glucose or mannitol	2.50
Or sorbitol or saccharose	for a sachet

Formula nº 2 - Granules	g
Trimethyl-carboxymethyl-ammonium anhydrous	10
Acetyl salicylic acid	10
Sodium benzoate	5
Magnesia	0.050
Orange spray	0.10
Saccharose, q.s.p	100

Formula nº 3 - Tablets	g
trimethyl-carboxymethyl-ammonium citrate	0.500
Acetyl salicylic acid	0.300
Magnesia	0.150

Sodium benzoate 0.100
Yellow tartrazine 0.001
Lemon spray.....0.002

Glucose or mannitol.....0.800
for a tablet

Formula n° 4 - Pills g
Trimethyl-carboxymethyl-
ammonium citrate.....0.200
Acetyl salicylic acid 0.300
Lithium benzoate 0.050
Magnesia.....0.100
Gluten coating q.s.p ..... 1 pill

Formula n° 5 - Effervescent tablets g
Trimethyl-carboxymethyl-
ammonium citrate.....0.500
Acetyl salicylic acid 0.300
Citric acid 0.900
Sodium carbonate acid .....0.120 to 0.150
Lithium carbonate 0.050
Sodium benzoate 0.100
Mandarine spray.....0.002
Yellow tartrazine 0.001
Glucose.....0.400
For an effervescent tablet

Formula n° 6 - Effervescent Powder g
Trimethyl-carboxymethyl-
ammonium anhydrous..... 25
Acetyl salicylic acid 15
Vitamin C 15
Calcium or magnesium carbonate.....17.50
Yellow tartrazine 0.010
Glucose or mannitol
Or sorbitol q.s.p 100

Formula n° 7 - Effervescent granules	g
Trimethyl-carboxymethyl-ammonium anhydrous	25
Acetyl salicylic acid	25
Calcium ascorbate	30
Calcium acid carbonate	20
Lemon spray	0.020
Yellow tartrazine	0.200
Saccharose, q.s.p	150

In a variation of formula 2, trimethyl carboxymethyl ammonium base and acetylsalicylic acid are advantageously replaced by the acetylsalicylate of carboxymethyl-trimethyl-ammonium in corresponding quantity. In addition, the anion citrate not bringing an essential element can be:
Either, deleted, the formulas being modified as in formula 2 alternative specified above;

Either, replaced by another pharmacologically acceptable anion, without going out of the scope of the invention.

Any other usual presentation, in particular in the form of capsules, could, of course, be adopted.

The therapeutic indications are essentially those of acetylsalicylic acid with an increased gastric tolerance allowing a higher dosage and a longer duration of treatment. Migraines accompanied by liver and digestive events constitute a particularly interesting indication for this type of combination therapy.

Applicants give below some clinical observations reports.

Case N°.1. -- M. A. .., 67 years old, has a polar upper right OA of the hip for 10 years. 1t is a little disabling form, but nevertheless needing - in this plethoric subject (82 kg for 1.67 m) - almost continuously a salicylic therapy. At 2.50 g/24 h efficient

dose, acetylsalicylic acid was unfortunately poorly supported and causes heartburn in addition to former dyspepsia.

The replacement of aspirin by the N°5 formula at equivalent dose (8 pills/day) completely wiped out this gastric intolerance and after three months of continuous treatment, the patient even reported improvement in the earlier dyspeptic state.

Case N°2. - Mrs. B. .., 49 years old, suffers from rheumatoid arthritis for 20 years. Walking is difficult and is done with two canes. The deformation of the hands and painful stiffening severely limit the function. Since the last 4 years, the patient receives corticosteroids (6 to 8 mg triamcinolone), and also takes 1 to 2 g per day acetylsalicylic; above this dose aspirin is poorly tolerated and causes burns with gastric cramps particularly worrisome in this patient treated with corticosteroids. The replacement of acetylsalicylic acid by formula N°. 5 has a very clear effect: gastralgies disappearance, even at dose corresponding to 3.50 g aspirin by twenty-four hours

The interest in this case is even greater than the removal of the gastric intolerance makes easier corticosteroid treatment monitoring.

Case N°. 3. -- Mrs. D. .., 48 years old, suffers from a right hemicrania past two years. The painful crisis lasts three or four hours and is followed by digestive manifestation events in type of nausea and heaviness in the right hypocondrus. Aspirin has only a partial effect on headache events and none on digestive disorders. The test of the formula N°5 is undertaken with equivalent dose of acetylsalicylic acid. The analgesic action appears substantially equal, but the patient reported mitigation GI symptoms post-critical ever achieved with acetylsalicylic acid alone.

ABSTRACT
The present invention relates to novel neuralgic associations with improved tolerance.

Preferably, the applicants associate with acetylsalicylic acid, trimethyl carboxymethylammonium free base or its pharmacologically acceptable salts, the association can also be obtained in the form of acetylsalicylate of carboxymethyl-trimethyl-ammonium.

The association can be made on a pharmaceutical support comporting elements susceptible to present other therapeutic indications.

The drugs, according to the present invention will be presented in any usual form and, notably in the form of powder, effervescent powder, granules, effervescent granules, tablets, effervescent tablets, pills and capsules.

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2.590M]
DOCUMENTARY OPINION ON THE NOVELTY

Documents likely to prejudice the novelty of the drug: none. Documents showing the state of the art in the field: French Patent (B.S.M.), N°. 1,123 M.